DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

IMMUNODIAGNOSTIC SYSTEMS LTD.
MICK HENDERSON
RA OFFICER
10 DIDCOT WAY, BOLDON BUSINESS PARK
BOLDON, TYNE & WEAR NE35 9PD, GREAT BRITAIN

August 25, 2015

Re: K142351
Trade/Device Name: 25-Hydroxy Vitamin D^S EIA
Regulation Number: 21 CFR 862.1825
Regulation Name: Vitamin D test system
Regulatory Class: II
Product Code: MRG
Dated: August 14, 2015
Received: August 19, 2015

Dear Mick Henderson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
k142351

Device Name
25-Hydroxy Vitamin DS EIA

Indications for Use *(Describe)*
The 25-Hydroxy Vitamin DS EIA assay is intended for the quantitative determination of 25-hydroxyvitamin D [25(OH)D] and other hydroxylated metabolites in human serum or plasma. Results are to be used in conjunction with other clinical and laboratory data to assist the clinician in the assessment of vitamin D sufficiency in an adult population.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) SUMMARY

510k Number **k142351**

Introduction According to the requirements of 21CFR807.92, the following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

Submitter

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Date prepared:18 August 2015

Device Name

Proprietary names: 25-Hydroxy Vitamin D^S EIA

Common names: Vitamin D test

Classification: 21CFR862.1825 Vitamin D Test System
Regulatory Class: II

Product Code: MRG

Predicate Device Name: IDS, OCTEIA 25-OH Vitamin D EIA, (k021163)

A. Test Principle:

The 25-Hydroxy Vitamin D^S EIA is a manual assay test and does not require the use of an automated system. The whole assay is performed in a microtitre plate and requires a user to perform each step.

The 25-Hydroxy Vitamin D^S EIA assay

The 25-Hydroxy Vitamin D^S assay is an enzymeimmunoassay for the quantitation of 25(OH)D and other hydroxylated metabolites in serum or plasma. 25µL of each calibrators, controls and samples are diluted with biotin labelled 25(OH)D. The diluted samples are incubated in microtitre wells which are coated with a highly specific sheep 25(OH)D at room temperature before aspiration and washing. Enzyme (horseradish peroxidase) labelled avidin, is added and binds selectively to complexed biotin and, following a further wash step, colour is developed using a chromogenic substrate (TMB).

The absorbance of the stopped reaction mixtures are read in a microtitre plate reader, colour intensity developed being inversely proportional to the concentration of 25(OH)D.

B. Indications For Use:

For In Vitro Diagnostic Use

The 25-Hydroxy Vitamin D^S EIA assay is intended for the quantitative determination of 25-hydroxyvitamin D [25(OH)D] and other hydroxylated metabolites in human serum or plasma. Results are to be used in conjunction with other clinical and laboratory data to assist the clinician in the assessment of vitamin D sufficiency in an adult population.

Rx Only

C. Comparison with the predicate:

Similarities compared to the chosen predicate device (OCTEIA 25-hydroxy vitamin D EIA)

	Predicate K021163	**Candidate Device**
Intended Use	The OCTEIA 25-hydroxy vitamin D EIA (25-OH D) kit is an assay for the quantitative measurement of 25-Hydroxy vitamin D in serum and plasma.	Same
Indications for use	Results are to be used in conjunction with other clinical and laboratory data to assist the	Same

	clinician in the assessment of vitamin D sufficiency	
Analyte	25-hydroxy vitamin D	Same
Reagent storage	2-8^{o}C	Same
Capture	Antibody coated micro plate	Same
Calibrator	Low charcoal stripped human serum containing 25-hydroxy vitamin D and sodium azide as a preservative	Same
Sample volume	25µL	Same
Units	nmol/L	Same
Kit components	EIA kit consisting of Anti-25-OH D coated plate, Biotinylated 25-OH D, Standards (7 levels), kit controls (2 levels), Avidin HRP solution, substrate solution, stop solution and wash solution	Same
Calibration	Full standard curve to be run with all assays	Same
Calibration interval	Per assay run	Same
Quality Control	Two (2) controls provided	Same
Conversion of units	nmol/L x 0.40 = ng/mL ng/mL x 2.5 = nmol/L	Same

Differences compared to the chosen (FDA cleared; marketed) predicate device

	Predicate K021163	**Candidate Device**
Antibodies	Sheep anti 25-hydroxy vitamin D.	new source
Analytical sensitivity	5 nmol/L	NA
Functional Sensitivity (Limit of Quantitation (LoQ)	NA	4.8ng/mL (12 nmol/L)
Limit of Detection (LoD)	NA	2.7ng/mL (6.9 nmol/L)
Limit of Blank (LoB)	NA	1.3ng/mL (4.5nmol/L)
Precision	Intra-assay Precision n = 10 5.3% to 6.7% in the concentration range 39 to 165nmol/L Inter-assay Precision n = 11 4.6% to 8.7% in the concentration range 40 to 132nmol/L	Within Run Precision n = 88 1.9% to 3.7% in the concentration range 11.7 to 65.1 ng/mL (29.3 to 183 nmol/L) Total Precision n = 88 3.7% to 11.6% in the concentration range 11.7 to 65.1ng/mL (29.3 to 183 nmol/L)

Specificity, Interfering substances & Cross Reactivity	Specificity 25-Hydroxy vitamin D_3 100%	Specificity 25-Hydroxy vitamin D_3 95%

Performance	**Predicate K021163**	**Candidate Device**
Specificity, Interfering substances & Cross Reactivity	Interference: Haemoglobin Tested up to 1470 mg/dL Bilirubin Tested up to 513 µmol/L Lipid Tested up to 5.6 mmol/L triglyceride	Interference: Haemoglobin No interference up to 400mg/dL Bilirubin, conjugated No interference up to 20mg/dL Triglyceride (Intra Lipid) No interference up to 475mg/dL Total Protein No interference up to 9.2g/dL HAMA No interference up to 1000ng/mL Red Blood Cells No interference up to 0.4% Rheumatoid Factor No interference up to 800IU/mL Vitamin D Binding Protein (Gc globulin) No interference up to 2000 ng/mL Cholesterol, Total No interference up to 500mg/dL Biotin No interference up to 200nmol/L

Performance	Predicate K021163	Candidate Device
	Cross Reactivity 25-Hydroxy vitamin D_2 75% 24,25-DiHydroxy vitamin D_3 ≥ 100% Cholecalciferol (D_3) < 0.01% Cholecalciferol (D_2) < 0.30%	Cross Reactivity 25-Hydroxy vitamin D_2 109% 24-25 Di- Hydroxy vitamin D_3 95% 24,25-$(OH)_2D_3$ 91% 3-epi-25-OH Vitamin D_3 -1% 3-epi-25-OH Vitamin D_2 -1% 1,25-$(OH)_2D_3$ 5% 1,25-$(OH)_2D_2$ 84% Paricalcitol 17% 25(OH)D_3 95% 25(OH)D_2 109% Vitamin D3 (Cholecalciferol) 0% Vitamin D2 (Ergocalciferol) 6%

Performance	**Predicate K021163**	**Candidate Device**
Reference range/ Expected Values	47.7 – 144 nmol/L	Non Supplemented 11.2 to 45.9ng/mL 28.0 to 114.6 nmol/L Supplemented 15.4 to 86.8ng/mL 38.5 to 217.1 nmol/L Overall 12.3 to 49ng/mL 30.7 to 122.5 nmol/L
Method comparison	Against a recognised radioimmunoassay n = 180 AC57 = 1.01(x) + 0.7 Correlation coefficient (r) = 0.9	Against Predicate device n = 195 Passing Bablok regression: 25-Hydroxy Vitamin D^S= 0.88 x (25-Hydroxy Vitamin D) + 3.2 ng/mL (+ 8.1 nmol/L) Pearson correlation coefficient, r: 0.94
Reportable Range	2ng/mL to 152ng/mL	6.5 to 100ng/mL
Linearity	Mean Measured / Expected 102% *Range individual dilutions 88% to 125%*	Linear regression of the observed concentrations versus the expected concentrations: Observed = 1.02 x (Expected) + 0.23 ng/mL Observed = 1.02 x (Expected) + 0.58 nmol/L Regression coefficient R^2:= 1.00 Maximum deviation; -8.8% for samples > 20 ng/mL and 2.37 ng/ml for samples < 20 ng/mL
Sample matrix (primary tube type)	Serum or Plasma (EDTA or Heparin)	Serum (standard sampling tubes or tubes containing serum separating gel) or plasma (EDTA, lithium heparin, sodium heparin or sodium citrate)

D. Performance Characteristics :

1. Analytical performance:

a. Precision/Reproducibility:

Precision was determined in accordance with CLSI EP5-A2, "Evaluation of Precision Performance of Quantitative Measurement Methods". 10 serum samples were assayed using 3 lots of reagents in duplicate, twice per day for a minimum of 20 days ($n \geq 80$ replicates per sample).

Results from one representative lot is summarized in the table below (n=88)

ng/mL

			EP Evaluator							
			Within Run		Between Run		Between Day		Total	
	n =	Mean	SD	%cv	SD	%cv	SD	%cv	SD	%cv
IQC1	88	19.1	0.4	1.9%	0.6	3.2%	0.1	0.4%	0.7	3.7%
IQC2	88	43.7	0.8	1.9%	0.9	4.3%	0.0	0.0%	2.0	4.6%
IQC3	88	65.1	2.3	3.5%	4.0	6.2%	1.7	2.6%	4.9	7.6%
S1	88	11.7	0.4	3.4%	1.3	11.0%	0.0	0.0%	1.4	11.5%
S2	88	24.5	0.6	2.5%	1.3	5.3%	0.0	0.0%	1.4	5.8%
S3	88	40.7	1.0	2.5%	2.1	5.1%	0.0	0.0%	2.3	5.7%
S4	88	73.2	2.7	3.7%	4.0	5.5%	0.6	0.8%	4.9	6.6%
S5	88	21.7	0.5	2.4%	0.9	4.1%	0.0	0.0%	1.0	4.7%
S6	88	51.0	1.9	3.7%	3.4	6.6%	0.0	0.0%	3.9	7.6%
S7	88	28.3	0.8	2.7%	1.7	6.2%	0.0	0.0%	1.9	6.7%

b. Linearity/assay reportable range:

Linearity was evaluated based on a modified version of CLSI EP-6A, "Evaluation of the Linearity of Quantitative Measurement Procedures". Samples containing varying concentrations of 25-hydroxyvitamin D were assayed in replicate of four. The resulting mean concentrations were compared to predicted concentrations. Samples were prepared by diluting a high patient sample with a low patient sample prior to assay. The linear regression (weighted) of the Observed concentrations versus the expected concentrations is:

Observed = 1.02 x (Expected) + 0.23 ng/mL
Observed = 1.02 x (Expected) + 0.58 nmol/L
Regression coefficient R^2:= 1.00

Maximum deviation; -8.8% for samples > 20 ng/mL and 2.37 ng/ml for samples < 20 ng/mL

The reportable range of the assay is 6.5 – 100 ng/mL (16.3 – 250 nmol/L). Any value that reads below 6.5 ng/mL (16.3nmol/L) should be reported as "< 6.5 ng/mL (16.3 nmol/L)".

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability:

The 25-Hydroxy Vitamin D^S assay is traceable to the isotope dilution-liquid chromatography/tandem mass spectrometry (ID-LCMS/MS) 25(OH) Vitamin D reference method procedure (RMP) which was used in assigning the target value for the Vitamin D Standardization Program (VDSP single donor human serum panel. The ID-LCMS/MS RMP is traceable to the National Institute of Standards and Technology Standard Reference Material (SRM) 2972.

The 25-Hydroxy Vitamin D^S assay is certified by the CDC Vitamin D Standardization Certification Program (VDSP) http://www.cdc.gov/labstandards/hs.html

Stability

This kit is stable for 8 months when stored at 2-8°C.

Kit component	**After opening or preparation (open vial stability)**
Biotin 25(OH)D Solution	8 weeks after reconstitution Store at 2-8ºC in the dark immediately after use
Unused Ab. coated plate strip	8 weeks Store at 2-8ºC in foil pouch with desiccant sachet
Calibrators, Controls	8 weeks Store at 2-8ºC after opening
Wash Solution	8 weeks Store at room temperature (18-25 ºC) after preparation

d. Detection limit:

The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) were determined based on guidance from CLSI EP17-A "Protocols for the determination of limits of detection and limits of quantitation".

Sensitivity	**25OHD Levels**
LoB	1.3 ng/mL (4.5 nmol/L)
LoD	2.7 ng/mL (6.9 nmol/L)
LoQ	4.8 ng/mL (12.0 nmol/L)

e. Analytical specificity:

Cross-reactivity of endogenous 25(OH) vitamin D metabolite. Endogenous 25(OH) vitamin D metabolites were spiked into vitamin D serum samples and analyzed with the 25-Hydroxy Vitamin D^S assay.

Cross Reactant	Spike Conc. (ng/mL)	Mean % Cross Reactivity
25(OH)D_3	10.0	95%
	20.0	
25(OH)D_2	10.0	109%
	20.0	
24,25-$(OH)_2D_3$	4.0	91%
	6.0	

Cross-reactivity of exogenous synthetic 25(OH) vitamin D metabolite. Exogenous synthetic 25(OH) vitamin D metabolites were spiked into vitamin D serum samples and analyzed with the 25-Hydroxy Vitamin D^S assay.

Cross Reactant	Spike Conc. (ng/mL)	Mean% Cross Reactivity
3-epi-25(OH) D_3	100	-1%
3-epi-25(OH) D_2	100	-1%
1,25-$(OH)_2D_3$	2	5%
1,25-$(OH)_2D_2$	20	84%
VitaminD_3 (Cholecalciferol)	1000	0%
VitaminD_2 (Ergocalciferol)	100	6%
Paricalcitol*	100	17%

***** Paricalcitol interferes with the 25-Hydroxy Vitamin D^S EIA test. Paricalcitol, when tested, caused a positive bias in sample result.

The following substances do not interfere in the 25-Hydroxy Vitamin D^S EIA assay when the concentrations presented in the following table are below the stated threshold.

Potentially Interfering Agent	Threshold Concentration
Triglycerides	475 mg/dL
Bilirubin (conjugated)	20 mg/dL
Haemoglobin	400 mg/dL
HAMA	1000 ng/mL
Rheumatoid Factor	800 IU/mL
Red Blood Cells	0.40%
Vitamin D Binding Proteins	2000 ng/dL

Total Protein	9.2g/dL
Cholesterol, Total	500 mg/mL
Biotin	200nmol/L

2. Comparison studies:

a. Method comparison with predicate device:

The 25-Hydroxy Vitamin D^S EIA Assay was compared against the 25-Hydroxy Vitamin D EIA assay (K021163) for the quantitative determination of 25-Hydroxy Vitamin D (and other hydroxylated metabolites), following CLSI EP-9A2, "Method Comparison and Bias Estimation Using Patient Samples".

Correlation to 25-Hydroxy Vitamin D EIA, AC57 (k021163)

Passing Bablok	y = 0.88x + 3.23 ng/mL	y = 0.88 + 8.05 nmol/L
Slope, 95% Confidence Interval	0.86 to 0.91	0.86 to 0.91
Intercept, 95% Confidence Interval	2.71 to 3.83 ng/mL	6.85 to 9.45 nmol/L
Linear Regression	y = 0.82x + 4.86 ng/mL	y = 0.82x + 12.35 nmol/L
Slope, 95% Confidence Interval	0.80 to 0.84	0.80 to 0.84
Intercept, 95% Confidence Interval	4.14 to 5.57 ng/mL	10.35 to 13.92 nmol/L
Correlation Coefficient, r	0.97	0.97
n	195	195
Diffrence Plot	-0.61	-1.53

Additional method comparison study was performed against the reference measurement procedure using 109 in dependent native serum samples which has been value assigned by the Ghent reference method procedure. Regression analysis was summarized below:

	ng/mL	**nmol/L**
Passing Bablok	y = 0.96x - 0.11 ng/mL	y = 0.96x - 0.34 nmol/L
Slope, 95% Confidence Interval	0.88 to 1.02	0.88 to 1.02
Intercept, 95% Confidence Interval	-1.62 to 1.88 ng/mL	-4.15 to 4.68 nmol/L
Deming Regression	y = 0.97x - 0.84 ng/mL	y = 0.97x - 2.07 nmol/L
Slope, 95% Confidence Interval	0.90 to 1.04	0.90 to 1.04
Intercept, 95% Confidence Interval	-2.75 to 1.08 ng/mL	-6.85 to 2.71 nmol/L
Correlation Coefficient, r	0.947	0.947
n	109	109
Diffrence Plot	-1.77	-4.42

b. Matrix comparison:

Summary of the statistical methods used for alternative blood tube types to serum blood tube using a paired tube comparison is shown below.

Passing-Bablok analysis of the test and comparator assays was performed, taking the slope, intercept and correlation coefficient (with 95 % confidence intervals) and difference bias plot.

	SST	EDTA	Sodium Heparin
n	28	38	28
Passing bablok	y=0.99x+0.18 g/mL	y=0.97x+0.60ng/mL	y=1.07x-0.47ng/mL
Slope,95% confidence level	0.95 to 1.03	1.00 to 1.01	1.00 to 1.10
Intercept, 95% confidence level	-0.17 to 0.65ng/mL	-0.15 to 1.04ng/mL	-1.21 to 0.68ng/mL
Correlation Coefficient, r	0.99	1.00	0.99
Mean Bias	0.41	0.07	1.11

	Lithium Heparin	Citrate
n	28	28
Passing Bablok	Y=1.04x -0.22 ng/mL	Y=1.03x -0.70 ng/mL
Slope, 95% confidence level	1.01 to 1.08	0.98 to 1.06
Intercept, 95% Confidence level	-0.73 to 0.60 ng/mL	-1.36 to 0.49 ng/mL
Correlation Coefficient, r	1.00	0.99
Mean Bias	1.50	0.43

The design criterion was that the slope must be 0.85 to 1.15 and the intercept +/- 7 ng/mL and r $\geq$0.90.

Serum separator tubes (SST), EDTA plasma, Sodium Heparin plasma, Lithium Heparin plasma and citrate plasma tube data do not present any new issues of safety or effectiveness for the 25-Hydroxy Vitamin D^S EIA assay.

3. Expected values/Reference range:

An expected values study performed according to the non-parametric method in CLSI protocol C28-A2.

Samples from 280 apparently light skin and dark skin healthy male adults (71.1%) and female adults (28.9%) aged 21-77 years living in geographical diverse regions of the United States to represent a broad spectrum of UV light exposure in the intended population were assayed in the 25-Hydroxy Vitamin D^S Assay. Samples were from individuals with normal values for intact PTH, calcium, phosphate, and TSH, and not taking any interfering medications. The following ranges were determined using the 25-Hydroxy Vitamin D^S assay and are provided for information only. The 95 % reference interval for apparently healthy adults, were calculated by a non-parametric

method following guidance from CLSI C28-A3 " Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory".

Obtained normal adults range:12.3 to 49.0 ng/mL (30.7 to 122.5 nmol/L) (n=280)

Observed sample ranges were:

	n	%	Observed Sample Range (ng/mL)	Median (ng/mL)
Non-supplemented	219	78.2%	11.2 to 45.9	25.1
Northern US	*116*	*41.4%*	*10.3 to 35.1*	*22.6*
Southern US	*103*	*36.8%*	*14.6 to 48.0*	*29.5*
Supplemented	61	21.8%	15.4 to 86.8	30.2
Overall	280	100%	12.3 to 49.0	26.0

	n	%	Observed Sample Range (nmol/L)	Median (nmol/L)
Non-supplemented	219	78.2%	28.0 to 114.6	62.8
Northern US	*116*	*41.4%*	*25.6 to 87.6*	*56.5*
Southern US	*103*	*36.8%*	*36.6 to 120.0*	*73.9*
Supplemented	61	21.8%	38.5 to 217.1	75.5
Overall	280	100%	30.7 to 122.5	65.0

The above ranges should be considered as guidelines only; it is recommended that each laboratory establish its own expected range based for its own patient population.

The 95% reference interval was calculated by a non-parametric method following C28-A2. The following range was obtained:

Normal Adults 12.3 to 49.0 ng/mL (n = 280)
30.7 to 122.5 nmol/L (n = 280)

The package insert states that there is no universal agreement on the optimal concentration of 25OHD. Ranges should be based on clinical decision values that apply to both sexes of all ages rather than population based reference ranges for 25OHD.

E. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.